

SYNTHESIS OF 1-SUBSTITUTED ISOQUINOLINES; N-ACYLATION, PHOSPHONATION,  
WITIG REACTION, MORPHINE INTERMEDIATES

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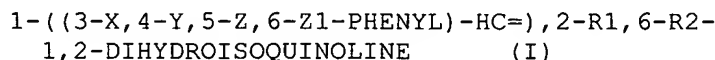
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#### Abstract:

A method for the synthesis of particular isoquinoline compounds which are useful intermediates in the preparation of members of the family of opium alkaloids, such as morphine and codeine. Steps in the process include the acylation of the isoquinoline nitrogen; reaction of the acylated isoquinoline with a phosphorous compound; and condensation with a benzaldehyde derivative to yield a 1-benzyl isoquinoline.

#### Exemplary Claim:

1. A METHOD OF PREPARING A MORPHINE INTERMEDIATE OF THE FOLLOWING FORMULA (I):



WHEREIN R1 IS COR GROUP WHEREIN R IS C1-6 ALKYL, PHENYL, OR C1-6 ALKOXY; R2 IS HYDROGEN OR C1-6 ALKOXY; X AND Z, WHICH MAY BE THE SAME OR DIFFERENT, ARE HYDROGEN, HYDROXY, SILYLOXY, HALOGEN, LOWER ALKOXY, PHENOXY, LOWER ALKYL, TRIMETHYLSILOXY, PHENYL, OR BENZYL; Y IS HYDROXY, SILYLOXY, HALOGEN, LOWER ALKOXY, PHENOXY, PHENYL, OR LOWER ALKYL; Z1 HYDROGEN OR HALOGEN, COMPRISING THE FOLLOWING STEPS (I) REACTING AN ISOQUINOLINE OF THE FOLLOWING FORMULA (II):

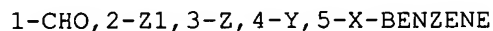


WHEREIN R2 IS AS DEFINED ABOVE, WITH A COMPOUND OF THE FORMULA LG-R1, WHEREIN LG IS MERCAPTO, HYDROXY, HALOGENO, LOWER ALKOXY, OR LOWER ALKYLTHIO AND R1 IS AS DEFINED ABOVE, FOLLOWED BY (II) REACTING THE N-ACYLATED PRODUCT OF STEP (I) WITH A PHOSPHORUS COMPOUND CAPABLE OF

BEING DISPLACED FROM THE COMPOUND OF THE FOLLOWING FORMULA (III) AS THE PHO MOIETY BY A WITTIG REACTION USING N-BUTYL LITHIUM AND ISOVANILLIN, TO YIELD A COMPOUND OF THE FOLLOWING FORMULA (III):



WHEREIN PHO IS A PHOSPHONATE PO(OR)2 WHEREIN R IS LOWER ALKYL. R1 AND R2, ARE AS DEFINED ABOVE; AND (III) REACTING THE COMPOUND OF FORMULA (III) IN A WITTIG REACTION WITH THE BENZALDEHYDE OF THE FOLLOWING FORMULA (IV):



WHEREIN X, Y, Z, AND Z1 ARE AS DEFINED ABOVE, TO YIELD A COMPOUND OF FORMULA (I).

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